

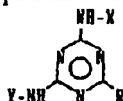
(57) (Abstract).

Object

To put forward novel 2,4-diamino-1,3,5-triazine derivatives.

Construction

This invention relates to compounds represented by the following formula:



(in the formula, X and Y denotes hydrogen atom or acyl group, R denotes phthalidylmethyl group, 2-(3,5-di(lower alkyl)-4-hydroxyphenyl)ethenyl group or the like).

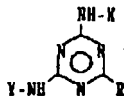
Effect

In accordance with this invention, new 2,4-diamino-1,3,5-triazine derivative is put forward which is useful as leukotriene antagonist.

Patent Claims

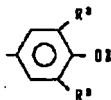
Claim 1

2,4-diamino-1,3,5-triazine derivatives represented by the following formula (1) or salt thereof



(1)

[In the formula, X and Y may be the same or different and denote hydrogen atom or acyl group; R denotes phenyl group, phthalidylmethyl group, a group represented by the following formula (2)



(2)

(in the formula, R2 and R3 denote lower alkyl group and Z denotes hydrogen atom or lower alkoxy-lower alkyl group)

or a group represented by the following formula (3)

-A-R1 (3)

(in the formula, A denotes -CH2-CH2- or -CH=CH-; R1 denotes phenyl group substituted by at least one substituent selected from the group comprising hydroxy group, cyano group, lower alkoxy group, lower alkoxycarbonyl group, phenyl group, phenoxy group,

benzyloxy group, and phenoxy substituted by trifluoromethyl group or lower alkyl group; naphthyl group, 3-bromophenyl group, 3-fluorophenyl group, 2,5-difluorophenyl group, 2-trifluoromethylphenyl group, 3-trifluoromethylphenyl group, 4-trifluoromethylphenyl group, 3,5-bis(trifluoromethylphenyl) group, 4-lower alkyl phenyl group, 3,5-di(lower alkyl)-4-hydroxy phenyl group, 3-pyridyl group or 6-methyl-3-pyridyl group); however, when R denotes phenyl group, and R1 denotes 3-trifluoromethylphenyl group, then X and/or Y denotes acyl group; and when R1 denotes 3-pyridyl group, then X and Y denote nicotinoyl group or 2-trifluoromethylbenzoyl group].

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention.

This invention relates to novel 2,4-diamino-1,3,5-triazine derivatives.

(0002)

Technology of the Prior Art.

As far as leukotriene is concerned, its biological significance has been widely researched, and in particular the significance thereof has been reported in various diseases such as neonatal anoxia, pulmonary circulation hypertension, adult respiratory distress syndrome, psoriasis, spondylarthritis, rheumatoid arthritis, gout, inflammatory enteritis or the like, and the leukotriene antagonist that displays antagonism to leukotriene is useful as therapeutic or preventive agent of allergic diseases, inflammatory diseases, cardiovascular disorder or the like.

(0003)

On the other hand, as far as 2,4-diamino-1,3,5-triazine derivatives are concerned, an application as antiulcerative agent has been reported (Kokai 2-223566, Kokoku 55-4751), however, there is no report whatsoever about the action on leukotriene.

(0004)

Problems to be Overcome by this Invention

This invention has an object of putting forward novel 2,4-diamino-1,3,5-triazine derivatives which exhibit leukotriene antagonism.

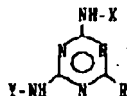
(0005)

Means to Overcome these Problems

This invention relates to 2,4-diamino-1,3,5-triazine derivatives represented by the

following formula (1) or salt thereof.

(0006)

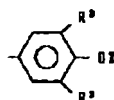


(1)

(0007)

[In the formula, X and Y may be the same or different and denote hydrogen atom or acyl group; R denotes phenyl group, phthalidylmethyl group, a group represented by the following formula (2)

(0008)



(2)

(0009)

(in the formula, R2 and R3 denote lower alkyl group and Z denotes hydrogen atom or lower alkoxy-lower alkyl group)

or a group represented by the following formula (3)

-A-R1 (3)

(in the formula, A denotes -CH₂-CH₂- or -CH=CH-; R1 denotes phenyl group substituted by at least one substituent selected from the group comprising hydroxy group, cyano group, lower alkoxy group, lower alkoxycarbonyl group, phenyl group, phenoxy group, benzyloxy group, and phenoxy substituted by trifluoromethyl group or lower alkyl group; naphthyl group, 3-bromophenyl group, 3-fluorophenyl group, 2,5-difluorophenyl group, 2-trifluoromethylphenyl group, 3-trifluoromethylphenyl group, 4-trifluoromethylphenyl group, 3,5-bis(trifluoromethyl)phenyl group, 4-lower alkyl phenyl group, 3,5-di-(lower alkyl)-4-hydroxy phenyl group, 3-pyridyl group or 6-methyl-3-pyridyl group);

however, when R denotes phenyl group, and R1 denotes 3-trifluoromethylphenyl group, then X and/or Y denotes acyl group; and when R1 denotes 3-pyridyl group, then X and Y denote nicotinoyl group or 2-trifluoromethylbenzoyl group].

(0010)

As the acyl group represented by X or Y in the aforesaid formula (1), for example, acetyl group, and substituted or unsubstituted nicotinoyl group or benzoyl group or the like can be nominated. In this specification, lower alkyl group denotes alkyl group of carbon number 1-6, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl

group, tert-butyl, sec-butyl group, pentyl group, hexyl group or the like; lower alkoxy group denotes alkoxy group of carbon number 1-6, for example, methoxy group, ethoxy group, propoxy group or the like; lower alkoxy-carbonyl group denotes alkoxy-carbonyl group of carbon number 1-6, for example, methoxycarbonyl group, ethoxycarbonyl group or the like; lower alkoxy-lower alkyl group denotes alkoxy-alkyl group of carbon number 1-6, for example, methoxymethyl group or the like.

(0011)

Among the compounds represented by the aforesaid formula (1), the compounds in which R is $-\text{CH}=\text{CH}-\text{R}_1$, namely, compounds represented by the following formula (4):

(0012)



(0013)

can be produced by condensation of a compound represented by the following formula (5):

(0014)



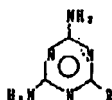
(0015)

with an aldehyde compound represented by R_1-CHO in the presence of acid or base. As the acid, for example, methanesulphonic acid, formic acid, sulphuric acid can be nominated, and as the base, for example, potassium hydroxide, sodium hydroxide, Triton B, sodium methoxide or the like can be nominated. When an acid is used, the reaction is usually carried out without solvent, however, when a base is used, solvent such as methanol, ethanol, 2-methoxyethanol is used. The reaction temperature is preferably 60-120°C, the reaction time is 1 hour to 7 days.

(0016)

Among the compounds represented by the aforesaid formula (1), the compounds in which R is $-\text{CH}_2\text{CH}_2-\text{R}_1$ can be produced by reducing the aforesaid compound (4) by conventional process. Among the compounds represented by the aforesaid formula (1), the compounds in which X and/or Y is acyl group can be produced by reacting the compound represented by the following formula (6):

(0017)

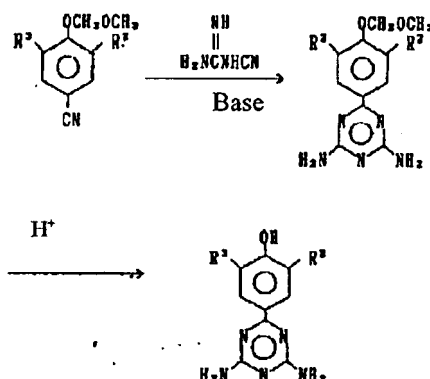


(8)

(0018)

with a corresponding acid chloride or acid anhydride in pyridine. The reaction temperature is 80-140°C, preferably 110-120°C, the reaction time is usually 3-8 hours. Among the compounds of this invention represented by the aforesaid formula (1), the compounds in which R is substituted or unsubstituted phenyl group can be produced by reacting corresponding benzonitrile derivative and dicyandiamide in the presence of base in accordance with the process of Kokoku 55-4751. In these circumstances, when Z in the aforesaid formula (2) is hydrogen atom, a process as illustrated below is preferably used wherein it is cyclized in a form in which the hydroxy group is protected as methoxymethoxy group, then it is converted to hydroxy group by treatment with acid.

(0019)

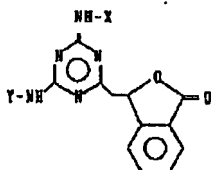


(0020)

(in the formula, R2 and R3 denote for example lower alkyl group)

Among the compounds of this invention represented by aforesaid formula (1), compounds in which R is phthalidylmethyl group, namely compounds represented by the following formula (7):

(0021)



(7)

(0022)

can be produced by reacting the aforesaid compound (5) with a compound represented by the following formula 8):

(0023)



(0024)

(in the formula, R₄ denotes hydrogen atom or lower alkyl group) in the presence of acid.
Moreover, by reacting a compound represented by the following formula (9):

(0025)



(0026)

and an acid chloride represented by the following formula (10):

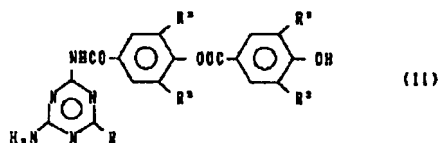
(0027)



(0028)

(in the formula, R₂ and R₃ have the same meanings as aforesaid),
compounds represented by the following formula (11)

(0029)



which are included in compounds of this invention represented by aforesaid formula (1)
can be produced.

(0030)

The compounds represented by aforesaid formula (1) which are the compounds of this
invention or salts thereof, for example, hydrochloride, maleate, fumarate, show

antagonism to leukotriene and are useful as therapeutic or preventive agent of allergic diseases, inflammatory diseases, cardiovascular disorder or the like.

(0031)

Next, administration and pharmaceutical formulation of the compounds of this invention will be explained. The compound of general formula (1) can be administered as it is or together with conventional pharmaceutical carrier to animals or humans. The administration forms are not limited in particular, and can be suitably selected in accordance with requirements, and oral agents such as tablets, capsules, granules, fine granules, powder or the like, parenteral agents such as injection, suppository or the like can be nominated.

(0032)

In order to display the desired effect as an oral agent, although the quantity differs depending on the age of the patient, severity of disease, but usually for an adult, the compound of general formula (1) 0.2-25 mg/kg body wt is preferably administered once or several times per day. The compound of this invention can be formulated into preparation such as liquid agent, powder, granules tablet, enteric coated agent, capsule or the like in accordance with conventional agent production method using suitable solvent, excipient, adjuvant or the like used for the preparation, and this can be orally or parenterally administered.

(0033)

For the prescription, combined agent with other medically active component can be formed. For the purpose of oral administration, table, pill, capsule, powder granules or the like can be prescribed using at least one type of excipient, for example, starch, lactose, sucrose, mannitol, carboxymethyl cellulose or the like. In this type of agent, in addition to aforesaid excipient, for example, lubricant such as magnesium stearate, sodium laurylsulphate, talc or the like, binder such as dextrin, crystalline cellulose, polyvinylpyrrolidone, gum Arabic, corn starch, gelatine or the like, disintegration agent such as sodium carboxy cellulose, potato starch, carboxymethyl cellulose or the like, fluidity promoter such as light anhydrous silicic acid can be suitably used. Moreover, the drug which has the the compound of this invention as effective component can be administered as suspension, emulsion, syrup, elixir, and these agents may contain corrigent filler and colouring agent.

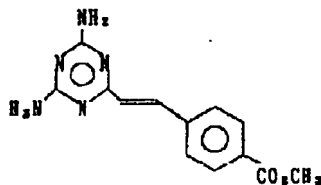
(0034)

Examples

Below this invention is explained in greater detail with Examples, Test Examples and Preparation Examples, however, the scope of this invention is not limited to these.

Example 1

2,4-diamino-[E]-6-[2-(4-methoxycarbonylphenyl) ethenyl]-1,3,5-triazine (compound 18)
(0035)



(0036)

2,4-diamino-6-methyl-1,3,5-triazine 5 g (40 mM) was dissolved in 50 ml formic acid, thereto was added 6.56 g (40 mM) 4-formylbenzoic acid methyl ester, and the mixture was heated under reflux for 91 hours. The reaction liquor was concentrated under reduced pressure, thereafter, was made alkaline with addition of saturated sodium hydrogen carbonate, the precipitated crystals were recovered by filtration, washed with water, thereafter, re-crystallised from a mixed solvent of 2-methoxyethanol and ethanol, and thereby the title compound (4.58 g 42.3 %) was obtained.

Melting point: 258°C (Decomposition)

¹H-NMR (200 MZ) δ (DMSO-d₆): 3.87 (3H, s), 6.67 (4H, br s), 6.86 (1H, d, J = 15.9 Hz), 7.76 (2H, d, J = 8.5 Hz), 7.82 (1H, d, J = 15.9 Hz), 7.97 (2H, d, J = 8.5 Hz).

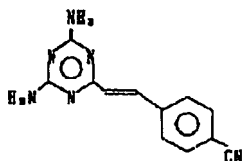
MS m/z (%) [EI]: 271 (M⁺, 65), 270 (100), 228 (37), 128 (21).

Example 2 and 3

The following compounds were synthesised by the same method as in Example 1.

Example 2

2,4-diamino-[E]-6-[2-(4-cyanophenyl) ethenyl]-1,3,5-triazine (compound 19)
(0037)



(0038)

Yield: 17.9 %

Melting point: >300°C (from 2-methoxyethanol)

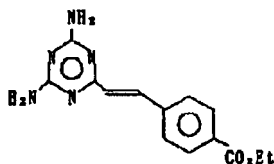
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.70 (4H, br s), 6.90 (1H, d, J = 15.9 Hz), 7.80 (1H, d, J = 15.9 Hz), 7.83 (4H, s).

MS m/z (%) [EI]: 283 (M⁺, 75), 237 (100), 195 (41), 169 (25).

Example 3

2,4-diamino-[E]-6-[2-(4-ethoxycarbonylphenyl) ethenyl]-1,3,5-triazine (compound 22)

(0039)



(0040)

Yield: 15.0 %

Melting point: 229.6-230.8°C (from ethanol)

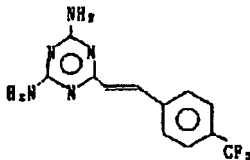
¹H-NMR (200 MZ) δ (DMSO-d₆): 1.34 (3H, t, J = 7.1 Hz), 4.33 (2H, q, J = 7.1 Hz), 6.68 (4H, br s), 6.87 (1H, d, J = 16.1 Hz), 7.76 (2H, d, J = 8.3 Hz), 7.82 (1H, d, J = 16.1 Hz), 7.97 (2H, d, J = 8.3 Hz).

MS m/z (%) [EI]: 285 (M⁺, 74), 284 (100), 256 (25), 242 (22).

Example 4

2,4-diamino-[E]-6-[2-(4-trifluoromethylphenyl) ethenyl]-1,3,5-triazine (compound 20)

(0041)



(0042)

2,4-diamino-6-methyl-1,3,5-triazine 5 g (40 mM) was dissolved in 28 ml methane sulphonic acid, thereto was added 5.5 ml (40 mM) 4-trifluoromethylbenzaldehyde, and the mixture was stirred at 110 °C for 2 hours. After cooling, dilute aqueous sodium

hydroxide was added to the reaction liquor to make it alkaline, and the precipitated crystals were recovered by filtration and washed with water, and thereafter, re-crystallised from ethanol, and thereby the title compound (6.09 g, 54.2 %) was obtained.

Melting point: 274.9-275.7°C.

¹H-NMR (200 MZ) δ (DMSO-d₆): 6.70 (4H, br s), 6.88 (1H, d, J = 15.9 Hz), 7.73 (2H, d, J = 8.3 Hz), 7.83 (1H, d, J = 15.9 Hz), 7.85 (2H, d, J = 8.3 Hz).

MS m/z (%) [EI]: 281 (M⁺, 93), 280 (100), 238 (54), 212 (28), 196 (22), 111 (26).

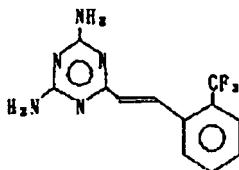
Examples 5-13

The following compounds were synthesised by the same method as in Example 4.

Example 5

2,4-diamino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine (compound 21)

(0043)



(0044)

Yield: 54.0 %

Melting point: 250.0-250.9°C (from ethanol).

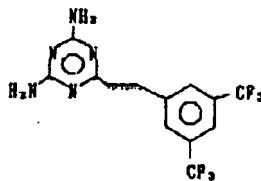
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.72 (4H, br s), 6.78 (1H, d, J = 15.9 Hz), 7.50-8.10 (4H, m), 8.11 (1H, brd, J = 15.9 Hz).

MS m/z (%) [EI]: 281 (M⁺, 100), 212 (76), 170 (53), 111 (32).

Example 6

2,4-diamino-[E]-6-[2-{3,5-bis(trifluoromethyl)phenyl} ethenyl]-1,3,5-triazine
(compound 24)

(0045)



(0046)

Yield: 50.6 %

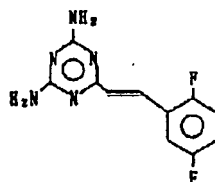
Melting point: 208.2-209.0°C (from ethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 6.68 (4H, br s), 7.08 (1H, d, J = 15.9 Hz), 7.89 (1H, d, J = 15.9 Hz), 8.00 (1H, br s), 8.33 (2H, br s).

MS m/z (%) [EI]: 349 (M⁺, 100), 348 (56), 330 (22), 280 (27) 111 (60).

Example 7

2,4-diamino-[E]-6-[2-(2,5-difluorophenyl) ethenyl]-1,3,5-triazine (compound 25)
(0047)



(0048)

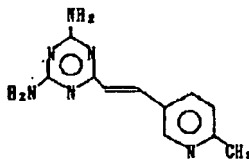
Melting point: >300°C (from 2-methoxyethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 6.71 (4H, br s), 6.89 (1H, d, J = 16.1 Hz), 7.20-7.40 (2H, m), 7.70-7.80 (1H, m), 7.90 (1H, br d, J = 16.1 Hz).

MS m/z (%) [EI]: 249 (M⁺, 57), 228 (100), 188 (29), 146 (20).

Example 8

2,4-diamino-[E]-6-[2-(6-methylpyridin-3-yl) ethenyl]-1,3,5-triazine (compound 26)
(0049)



(0050)

Yield: 36.6 %

Melting point: 253.7-254.3°C (from ethanol).

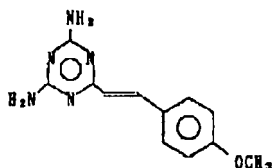
¹H-NMR (200 MZ) δ (DMSO-d₆): 2.49 (3H, s), 6.66 (4H, br s), 6.80 (1H, d, J = 15.9 Hz), 7.28 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 15.9 Hz), 7.99 (1H, dd, J = 8.3, 2.2 Hz), 8.63 (1H, d, J = 2.2 Hz).

MS m/z (%) [EI]: 228 (M⁺, 45), 227 (100), 185 (37), 144 (23).

Example 9

2,4-diamino-[E]-6-[2-(4-methoxyphenyl) ethenyl]-1,3,5-triazine (compound 32)

(0051)



(0052)

Yield: 27.4 %

Melting point: 244°C (decomposition) (from methanol).

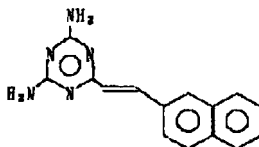
¹H-NMR (200 MZ) δ (DMSO-d₆): 3.79 (3H, s), 6.59 (4H, br s), 6.59 (1H, d, J = 15.9 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.75 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 243 (M⁺, 88), 242 (100), 200 (32), 158 (19).

Example 10

2,4-diamino-[E]-6-[2-(2-naphthyl) ethenyl]-1,3,5-triazine (compound 33)

(0053)



(0054)

Melting point: 237.8-238.4°C (from methanol).

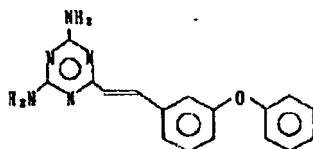
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.82 (4H, br s), 6.93 (1H, d, J = 15.9 Hz), 7.50-7.70 (2H, m), 7.80-8.20 (5H, m), 8.02 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 263 (M⁺, 100), 262 (96), 220 (44), 179 (21) 178 (36).

Example 11

2,4-diamino-[E]-6-[2-(3-phenoxyphenyl) ethenyl]-1,3,5-triazine (compound 34)

(0055)



(0056)

Melting point: 167.6-169.4°C (from methanol).

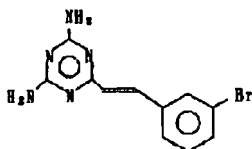
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.64 (4H, br s), 6.68 (1H, d, J = 15.9 Hz), 6.90-7.50 (9H, m), 7.73 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 305 (M+, 87), 304 (100), 262 (29), 220 (23).

Example 12

2,4-diamino-[E]-6-[2-(3-bromophenyl) ethenyl]-1,3,5-triazine (compound 35)

(0057)



(0058)

Yield: 59.9 %

Melting point: 188.9-189.7°C (from methanol-2-methoxyethanol).

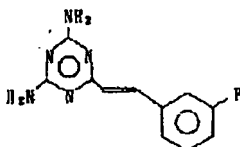
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.66 (4H, br s), 6.79 (1H, d, J = 15.9 Hz), 7.36 (1H, dd, J = 7.8, 7.8 Hz), 7.54 (1H, br d, J = 7.8 Hz), 7.63 (1H, br d, J = 7.8 Hz), 7.72 (1H, d, J = 15.9 Hz), 7.82 (1H, br s).

MS m/z (%) [EI]: 293 (M+, 77), 292 (100), 291(M+, 76), 290 (93), 250 (29), 248 (28) 128 (40).

Example 13

2,4-diamino-[E]-6-[2-(3-fluorophenyl) ethenyl]-1,3,5-triazine (compound 36)

(0059)



(0060)

Melting point: 275.9-276.8°C (from methanol-2-methoxyethanol).

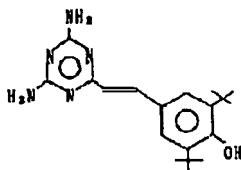
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.69 (4H, br s), 6.80 (1H, d, J = 15.9 Hz), 7.10-7.25 (1H, m), 7.30-7.55 (3H, m), 7.76 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 231 (M+, 76), 230 (100), 188 (45), 162 (28), 146 (22).

Example 14

2,4-diamino-[E]-6-[2-(3,5-di-t-butyl-4-hydroxyphenyl) ethenyl]-1,3,5-triazine (compound 37)

(0061)



(0062)

2,4-diamino-6-methyl-1,3,5-triazine 2.5 g (20 mM) was dissolved in 75 ml formic acid, thereto was added 5.15 g (22 mM) 3,5-di-*t*-butyl-4-hydroxybenzaldehyde, and the mixture was heated under reflux for 168 hours. The reaction liquor was concentrated under reduced pressure, and the obtained residue was purified by silica gel flash chromatography (CHCl₃ : MeOH = 9 : 1), and thereafter, re-crystallised from 2-propanol, and the title compound (0.85 g, 12.5 %) was obtained.

Melting point: 253.3-255.7°C.

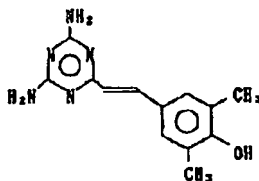
¹H-NMR (200 MZ) δ (CD₃OD): 1.45 (18H, s), 6.59 (1H, d, J = 15.9 Hz), 7.41 (2H, s), 7.85 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 342 (M++1, 24), 341 (M+, 99), 327 (23), 326 (100), 270 (18).

Example 15

2,4-diamino-[E]-6-[2-(4-hydroxy-3,5-dimethylphenyl) ethenyl]-1,3,5-triazine (compound 49)

(0063)



(0064)

The title compound was synthesised by the same method as in Example 14.

Yield: 18.7 %

Melting point: 285.9-288.1°C (decomposition) (from 2-propanol-methanol).

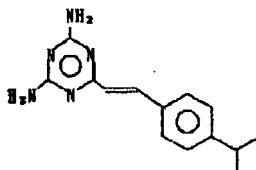
¹H-NMR (200 MZ) δ (DMSO-d₆): 2.19 (6H, s), 6.50 (1H, d, J = 15.9 Hz), 6.55 (4H, br s), 7.17 (2H, s), 7.66 (1H, d, J = 15.9 Hz), 8.12 (1H, s).

MS m/z (%) [EI]: 257 (M+, 100), 256 (70), 214 (25).

Example 16

2,4-diamino-[E]-6-[2-(4-isopropylphenyl) ethenyl]-1,3,5-triazine (compound 41)

(0065)



(0066)

2,4-diamino-6-methyl-1,3,5-triazine 1.25 g (10 mM) was dissolved in 20 ml 2-methoxyethanol, thereto were added 9.1 ml (20 mM) Triton B (40% methanol solution) and 3 ml (19.8 mM) 4-isopropylbenzaldehyde, and the mixture was stirred at 80 °C for 6.5 hours. After cooling, water was added and the precipitated crystals were collected by filtration and washed with water, and thereafter re-crystallised from the mixed solvent of 2-methoxyethanol and methanol, and the title compound (0.91 g, 35.7 %) was obtained.

Melting point: 247.8-248.8°C.

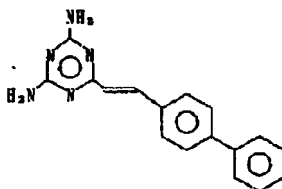
¹H-NMR (200 MZ) δ (DMSO-d₆): 1.21 (6H, d, J = 6.8 Hz), 2.91 (1H, m), 6.62 (4H, br s), 6.68 (1H, d, J = 16.1 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.53 (2H, d, J = 8.1 Hz), 7.77 (1H, d, J = 16.1 Hz).

MS m/z (%) [EI]: 255 (M⁺, 53), 254 (100), 240 (18), 212 (19), 156 (16).

Example 17

2,4-diamino-[E]-6-[2-(4-biphenyl) ethenyl]-1,3,5-triazine (compound 42)

(0067)



(0068)

2,4-diamino-6-methyl-1,3,5-triazine 1.25 g (10 mM) was dissolved in 30 ml 2-methoxyethanol, thereto were added 0.66 g (10 mM) KOH (85%) and 2.91 g (16 mM) 4-biphenylcarboxaldehyde, and the mixture was stirred at 90 °C for 16 hours. After cooling, water was added and the precipitated crystals were collected by filtration and washed with water, and thereafter, re-crystallised from 2-methoxyethanol, and the title compound (0.60 g, 20.7 %) was obtained.

Melting point: 276°C (decomposition) (from methanol - 2-methoxyethanol)

¹H-NMR (200 MZ) δ (DMSO-d₆): 6.66 (4H, br s), 6.79 (1H, d, J = 15.9 Hz), 7.35-7.75 (5H, m), 7.72 (4H, s), 7.84 (1H, d, J = 15.9 Hz).

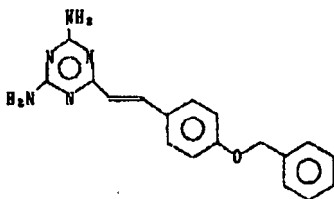
MS m/z (%) [EI]: 289 (M⁺, 82), 288 (100), 246 (34), 220 (13), 205 (16), 204 (31).

Examples 18-22

The following compounds were synthesised by the same method as in Example 17.

Example 18

2,4-diamino-[E]-6-[2-(4-benzyloxyphenyl) ethenyl]-1,3,5-triazine (compound 44)
(0069)



(0070)

Yield: 16.6 %

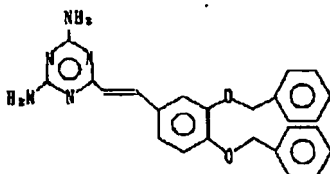
Melting point: 227.2-227.9°C (from methanol-2-methoxyethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 5.15 (2H, s), 6.58 (4H, br s), 6.59 (1H, d, J = 15.9 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.30-7.50 (5H, m), 7.56 (2H, d, J = 8.8 Hz), 7.74 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 319 (M⁺, 11), 228 (39), 91 (100), 78 (22).

Example 19

2,4-diamino-[E]-6-[2-(3,4-bis (benzyloxy) phenyl) ethenyl]-1,3,5-triazine (compound 45)
(0071)



(0072)

Yield: 54.6 %

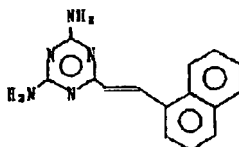
Melting point: 203.2-203.7°C (from methanol-2-methoxyethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 5.18 (2H, s), 5.22 (2H, s), 6.56 (4H, br s), 6.61 (1H, d, J = 15.9 Hz), 7.00-7.15 (2H, m), 7.25-7.55 (11H, m), 7.69 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 425 (M⁺, 5), 334 (17), 91 (100).

Example 20

2,4-diamino-[E]-6-[2-(1-naphthyl) ethenyl]-1,3,5-triazine (compound 46)
(0073)



(0074)

Yield: 27.8 %

Melting point: 220.1-221.2°C (from 2-methoxyethanol-methanol-ethyl acetate).

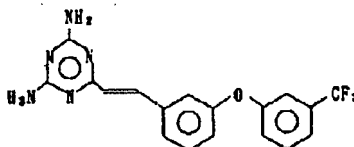
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.72 (4H, br s), 6.81 (1H, d, J = 15.9 Hz), 7.50-7.70 (3H, m), 7.90-8.05 (3H, m), 8.18 (1H, br d, J = 7.8 Hz), 8.64 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 263 (M⁺, 100), 262 (68), 220 (22), 178 (28).

Example 21

2,4-diamino-[E]-6-[2-{3-(3-trifluoromethoxyphenoxy) phenyl} ethenyl]-1,3,5-triazine (compound 47)

(0075)



(0076)

Yield: 42.6 %

Melting point: 204.7-205.8°C (from ethanol - 2-methoxyethanol).

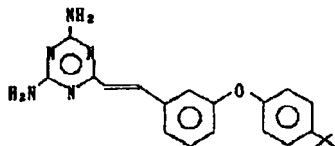
¹H-NMR (200 MZ) δ (DMSO-d₆): 6.63 (4H, br s), 6.72 (1H, d, J = 15.9 Hz), 7.00-7.70 (8H, m), 7.76 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 374 (M⁺⁺¹, 92), 373 (M⁺, 100), 330 (34), 289 (15), 112 (12).

Example 22

2,4-diamino-[E]-6-[2-{3-(4-t-butylphenoxy) phenyl} ethenyl]-1,3,5-triazine (compound 48)

(0077)



(0078)

Yield: 34.9 %

Melting point: 211.6-212.2°C (from ethanol).

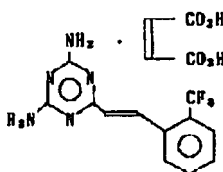
¹H-NMR (200 MZ) δ (DMSO-d₆): 1.30 (9H, s), 6.64 (4H, br s), 6.69 (1H, d, J = 15.9 Hz), 6.90-7.00 (3H, m), 7.20 (1H, br s), 7.30-7.50 (4H, m), 7.73 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 361 (M⁺, 64), 360 (38), 347 (25), 346 (100).

Example 23

2,4-diamino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine maleate (maleate of compound 21 (the compound of example 5))

(0079)



(0080)

0.5 g (1.77 mM) compound 21 was dissolved in 50 ml ethanol, thereto was added 0.25 g (2.15 mM) maleic acid, and the mixture was left to stand at room temperature for 0.5 hours. The precipitated crystals were collected by filtration and washed with ethanol, and the title compound (0.60 g, 85.7 %) was obtained.

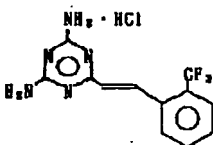
Melting point: 195.6-196.2°C (decomposition) (from ethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 6.21 (2H, s), 6.83 (1H, d, J = 15.9 Hz), 7.06 (4H, br s), 7.55-7.85 (3H, m), 7.99 (1H, d, J = 7.6 Hz), 8.15 (1H, brd, J = 15.6 Hz).

Example 24

2,4-diamino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine hydrochloride (hydrochloride of compound 21 (the compound of example 5))

(0081)



(0082)

0.5 g (1.77 mM) compound 21 was dissolved in 50 ml ethanol, thereto was added 0.3 g concentrated hydrochloric acid, and the mixture was left to stand at room temperature for 0.5 hours. The precipitated crystals were collected by filtration and washed with ethanol,

and the title compound (0.38 g, 67.9 %) was obtained.

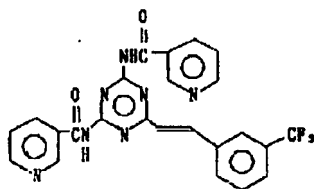
Melting point: >300°C (from ethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 7.01 (1H, d, J = 15.6 Hz), 7.60-7.90 (3H, m), 7.99 (1H, d, J = 7.6 Hz), 8.00-8.60 (4H, br), 8.29 (1H, br d, J = 15.6 Hz).

Example 25

2,4-bis (nicotinoylamino)-[E]-6-[2-(3-trifluoromethylphenyl) ethenyl]-1,3,5-triazine
(compound 23)

(0083)



(0084)

1 g (3.55 mM) 2,4-diamino-[E]-6-[2-(3-trifluoromethylphenyl) ethenyl]-1,3,5-triazine was dissolved in 35 ml pyridine, thereto was added 2.01 g (11.28 mM) nicotinoylchloride hydrochloride, and the mixture was heated under reflux for 4 hours. The reaction liquor was concentrated under reduced pressure, and saturated sodium bicarbonate was added and the mixture was made alkaline, and the precipitated crystals were collected by filtration and washed with water, and thereafter, re-crystallised from ethanol, and the title compound (0.75 g, 43.1 %) was obtained.

Melting point: 127-131°C.

¹H-NMR (200 MZ) δ (DMSO-d₆): 7.21 (1H, d, J = 15.9 Hz), 7.56 (2H, dd, J = 8.1, 4.9 Hz), 7.60-7.80 (2H, m), 7.90-8.10 (2H, m), 7.94 (1H, d, J = 15.9 Hz), 8.29 (2H, br d, J = 8.1 Hz), 8.78 (2H, dd, J = 4.9, 1.7 Hz), 9.08 (2H, d, J = 1.7 Hz).

MS m/z (%) [EI]: 491 (M⁺, 11), 386 (93), 385 (65), 357 (67), 106 (66), 78 (100).

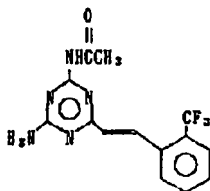
Examples 26-29

The following compounds were synthesised by the same method as in Example 25.

Example 26

2-acetyl-amino-4-amino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine
(compound 27)

(0085)



(0086)

Yield: 54.7 %

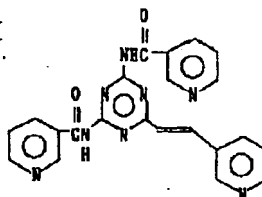
Melting point: >300°C (from 2-methoxyethanol).

MS m/z (%) [EI]: 323 (M⁺, 100), 281 (32), 212 (30), 170 (22).

Example 27

2,4-bis(nicotinoylamino)-[E]-6-[2-(3-pyridyl) ethenyl]-1,3,5-triazine (compound 28)

(0087)



(0088)

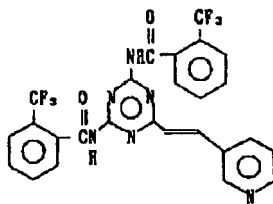
Melting point: 242-247°C (from 2-methoxyethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 7.18 (1H, d, J = 15.9 Hz), 7.48 (1H, dd, J = 8.1, 4.9 Hz), 7.56 (2H, dd, J=8.1, 4.9Hz), 7.91 (1H, d, J=15.9Hz), 8.20 (1H, br d, J = 8.1 Hz), 8.29 (2H, br d, J = 8.1 Hz), 8.60 (1H, br d, J = 4.9Hz), 8.78 (2H, br d, J = 4.9 Hz), 8.85 (1H, brs), 9.08(2H, br s). MS m/z (%) [EI]: 424 (M⁺, 49), 319(37), 318(100), 106(95), 78 (68).

Example 28

2,4-bis(2-trifluoromethylbenzoylamino)-[E]-6-[2-(3-pyridyl) ethenyl]-1,3,5-triazine (compound 29)

(0089)



(0090)

Yield: 28.0 %

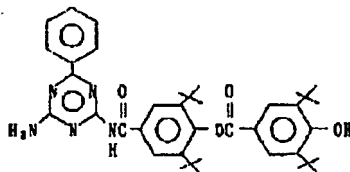
Melting point: 261.7-262.3°C (from ethyl acetate)

¹H-NMR (200 MZ) δ (DMSO-d₆): 6.83 (1H, d, J=16.1Hz), 7.03 (1H, d, J = 16.1 Hz), 7.45 (1H, dd, J = 8.1, 4.4 Hz), 7.60-7.90 (8H, m), 8.01 (1H, br d, J=8.1Hz), 8.58 (1H, br d, J = 4.4 Hz), 8.64 (1H, br s). MS m/z (%) [EI]: 558 (M⁺, 11), 489(35), 461(43), 433 (21), 173(100), 145(69).

Example 29

2-amino-4-{3,5-di-*t*-butyl-4-(3,5-di-*t*-butyl-4-hydroxybenzoyloxy)benzoylamino}-6-phenyl-1,3,5-triazine (compound 43)

(0091)



(0092)

Melting point: 167-170°C (from ethyl acetate).

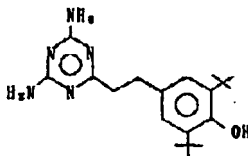
¹H-NMR (200 MZ) δ (DMSO-d₆): 1.32 (18H, s), 1.44 (18H, s), 7.30-7.60 (6H, m), 7.89 (2H, s), 7.99 (2H, s), 8.24-8.32 (2H, m).

MS m/z (%) [+FAB]: 652.4 (M⁺ +1), 233.2.

Example 30

2,4-diamino-6-[2-(3,5-di-*t*-butyl-4-hydroxyphenyl) ethyl]-1,3,5-triazine (compound 50)

(0093)



(0094)

2,4-diamino-[E]-6-(2-(3,5-di-t-butyl-4-hydroxyphenyl)ethenyl)-1,3,5-triazine (compound 37) 0.30 g (0.89 mM) was dissolved in a mixed liquid of 10 ml ethanol and 5 ml ethyl acetate, thereto was added 40 mg 5% Pd/C, and the mixture was stirred at room temperature for 168 hours at normal pressure to hydrogenate. The catalyst was removed by filtration and solvent was distilled off under reduced pressure, and thereafter, the residue was re-crystallised from ethyl acetate, to obtain the title compound (0.20 g, 66.6 %).

Melting point: 205.1-206.4°C.

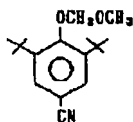
¹H-NMR (200 MZ) δ (DMSO-d₆): 1.35 (18H, s), 2.45-2.60 (2H, m), 2.75-2.85 (2H, m), 6.55 (4H, br s), 6.64 (1H, s), 6.88 (2H, s).

MS m/z (%) [EI]: 343 (M⁺, 92), 328(64), 272(65), 219(54), 126(44), 125(100).

Example 31

(1) 3,5-di-t-butyl-4-methoxymethoxybenzonitrile

(0095)



(0096)

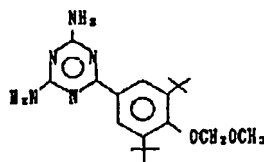
3,5-di-t-butyl-4-hydroxybenzonitrile 1.9 g (8.2 mM) was dissolved in 8 ml N,N-dimethylformamide, thereto was added 4.7 ml (29 mM) N-ethyldiisopropylamine, and the mixture was cooled. Methoxymethyl chloride (80%) 2.3 ml (21.4 mM) was added dropwise while cooling with ice and stirring, and thereafter, it was stirred at room temperature for 21 hours. Water was added, and extraction with ethyl acetate was performed, and after washing with water, it was dried with anhydrous sodium sulphate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel flash chromatography (hexane:ethyl acetate 40:1), to obtain the title compound as a yellow solid (1.43 g, 63.6 %).

(0097)

MS m/z: 276, 275 (M⁻), 230, 228, 188, 172, 45.

(2) 2,4-diamino-6-(3,5-di-t-butyl-4-methoxyphenyl)-1,3,5-triazine (compound 5)

(0098)



(0099)

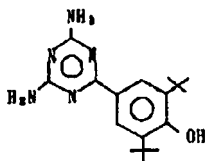
3,5-di-*t*-butyl-4-methoxybenzonitrile 1.41 g (5.1 mM) was dissolved in 8 ml 2-methoxyethanol, thereto were added dicyandiamide (90%) and potassium hydroxide (85%) 0.40 g (6.1 mM), and the mixture was heated under reflux for 20 hours. After cooling, water was added, and the precipitated crystals were collected by filtration and washed with water, to obtain the title compound (1.5 g, 82.0 %).

¹H-NMR (DMSO-*d*₆) δ: 1.44 (18H, s), 3.57 (3H, s), 4.89 (2H, s), 6.65 (4H, br s), 8.23 (2H, s).

Example 32

2,4-diamino-6-(3,5-di-*t*-butyl-4-hydroxy)phenyl-1,3,5-triazine (compound 38)

(0100)



(0101)

Compound (5) obtained in Example 31 (2) 1.45 g (4 mM) was dissolved in a mixture of 50 ml ethanol and 10 ml methanol, thereto was added 1.52 g (8 mM) *p*-toluene sulphonic acid monohydrate, and the mixture was heated under reflux for 1.5 hours. The reaction liquor was concentrated under reduced pressure, and saturated sodium bicarbonate was added to make it alkaline, and the precipitated crystals were collected by filtration and washed with water, to obtain the title compound (1.12 g, 89.0 %).

Melting point: >300°C.

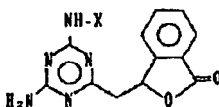
¹H-NMR (200 MZ) δ (DMSO-*d*₆): 1.43 (18H, s), 6.54 (4H, br s), 7.27 (1H, s), 8.12 (2H, s).

MS *m/z* (%) [EI]: 315 (M⁺, 48), 301(21), 300(100), 244(11).

Example 33

2,4-diamino-6-phthalidylmethyl-1,3,5-triazine (compound 17)

(0102)



(0103)

2,4-diamino-6-methyl-1,3,5-triazine 0.5 g (4 mM) was dissolved in 2.5 ml methane sulphonic acid, thereto was added 0.6 g (4 mM) 2-formylbenzoic acid, and the mixture was stirred at 110 °C for 3 hours. After cooling, dilute sodium hydroxide was added to make it alkaline, and the precipitated crystals were collected by filtration and washed with water, and thereafter, re-crystallised from ethanol, to obtain the title compound (0.10 g, 9.8 %). Melting point: 257.0-258.0°C (decomposition) (from ethanol).

¹H-NMR (200 MZ) δ (DMSO-d₆): 2.71 (1H, dd, J=8.8Hz), 3.12 (1H, dd, J=15.1, 4.9Hz), 6.10 (1H, dd, J=8.8, 4.9Hz), 6.72 (4H, br s), 7.60-7.90 (4H, m).

MS m/z (%) [EI]: 258(17), 257 (M⁺, 100), 229(59), 212(58), 152(59), 133(92), 105(55), 77(62).

Test Examples

As far as the compounds obtained in the following Examples are concerned, the following tests were carried out and the results obtained are shown in Table 1.

(0104)

Leukotriene C₄ antagonism test

Reagent: Leukotriene C₄ (Wako Pure Chemical Industries)

Histamine dihydrochloride (Wako Pure Chemical Industries)

Test animals: The gastric fundus of SD male rats with bodyweight about 250g (Nippon Charles River) was used.

Nutrient solution: Tyrode solution

NaCl 137.9 mM, KCl 2.7 mM, MgCl₂·6H₂O 0.5 mM, NaH₂PO₄·2H₂O 1.1 mM, CaCl₂·2H₂O 1.8 mM, NaHCO₃ 11.9 mM, glucose 5.6 mM.

Production of rat gastric fundus samples:

Immediately after sacrificing the SD rat by striking the back of the head and exsanguinating, laparotomy was performed and the lower part of the oesophagus and the upper part of the duodenum were each cut with scissors and it was removed, and immersed in prepared nutrient solution. The front of the stomach was cut free and cut

open vertically along a small curve, and scissor holes were introduced into the gastric fundus muscle pieces alternately at 3mm width, and this was cut further into lengths of 3 mm.

Magnus apparatus and measurement:

Sample was suspended in a Magnus tube containing 20 ml of tyrode solution, and a 1 g load was applied, and a set isotonic contraction was observed in acetylcholine 10^{-5} M, and it was washed, and after about 20 minutes, isotonic contraction (A) of leukotriene C_4 10^{-8} M was recorded as control contraction. Moreover, it was washed, and after about 30 minutes, test material was added, and after 10 minutes, leukotriene C_4 10^{-8} M was added and its isotonic contraction (B) was recorded.

Determination of activity:

$$\text{Inhibition rate (\%)} = (1-B/A) \times 100$$

Leukotriene D_4 antagonism test

Reagent: Leukotriene D_4 (Wako Pure Chemical Industries)

Histamine dihydrochloride (Wako Pure Chemical Industries)

Test animal: The ileum of Hartley male guinea pigs with bodyweight about 300g (Kiwa animal) was used.

Nutrient solution: Tyrode solution

NaCl 137.9 mM, KCl 2.7 mM, $MgCl_2 \cdot 6H_2O$ 0.5 mM, $NaH_2PO_4 \cdot 2H_2O$ 1.1 mM, $CaCl_2 \cdot 2H_2O$ 1.8 mM, $NaHCO_3$ 11.9 mM, glucose 5.6 mM.

Extraction of guinea pig ileum:

The guinea pigs were exsanguinated and laparotomised, and the ileum removed and its contents were washed and near 10 cm from near the caecum was removed, and suspended as a tubular sample of about 2 cm in a Magnus tube containing tyrode nutrient liquid at 32 °C with 95% O_2 5% CO_2 flowing through, and a 1 g load was applied.

Magnus apparatus and measurement:

After suspending the extracted sample, about every 20 minutes, and the Magnus tube was filled with nutrient liquid 20 ml at 32 °C with 95% O_2 5% CO_2 flowing through. A measurement record was observed of isotonic contraction in histamine solution 10^{-5} M

two times per set, it was washed, and after a further 20 minutes, as a control contraction, isotonic contraction (A) of leukotriene D₄ 10⁻⁸M was recorded. Furthermore, about 30 minutes after washing, test material was added, and after 10 minutes, leukotriene D₄ 10⁻⁸M was added and its isotonic contraction (B) was recorded.

Determination of activity:

$$\text{Inhibition rate (\%)} = (1 - B/A) \times 100$$

5-lipoxygenase inhibition test

RBL1 cultured cells were suspended in 50 mM phosphate buffer (pH7.4) containing 10% ethylene glycol and 1 mM ethylene diamine tetraacetic acid (EDTA), so as to have 5 x 10⁶ cells/ml, and subjected to ultrasound, then centrifugally separated at 10,000 x G for 10 minutes and 105,000 x G for a further 60 minutes, and the supernatant was taken as the 5-lipoxygenase enzyme sample.

(0105)

10 μM arachidonic acid as substrate, the enzyme sample obtained as above, and a DMSO solution of the compound obtained in the Examples, made to have final concentration 10 μM, were taken into a test tube and made to react for 10 minutes at 37 °C. Butyl 3,5-dinitrobenzoate 10 μl of 0.25M was added as an internal standard, and extraction with 1.8 ml of hexane was performed. The quantity of 5-HETE in this was measured by high-performance liquid chromatography [column, TSKgel ODS-80TM (TOYO SODA) with mobile phase of acetonitrile: water: ethyl acetate = 60:40:0.02, flow rate 1 ml/min, detection, UV (235 nm)].

(0106)

From the results, the 5-lipoxygenase inhibition rate was calculated according to the following formula

$$\text{Inhibition rate} = \{(C-S)/C\} \times 100 (\%)$$

C: 5-HETE peak area when compound obtained in an Example was not included (corrected using internal standard)

S: 5-HETE peak area when compound obtained in an Example was included (corrected using internal standard)

(0107)

Table 1

Compound number	leukotriene antagonism (%)			5-lipoxygenase inhibition (%)
	C ₄ (10μM)	D ₄		
		100μM	10μM	
19	49	18		
20	33		36	
21	69		6	
22	25	30		
23		59		
32		57		
33	55	72		
34	76		93	
35	38		19	
36	42			
37		100	92	100
38		82		68
41		99		
42		36		
43				
45		29		
46		100		
47			88	
48		69		
49		84		
50				
				63

(0108)

Preparation Example 1

Tablet preparation

(1)	2,4-diamino-[E]-6-{2-(3,5-di-t-butyl-4-hydroxyphenyl)ethenyl}-1,3,5-triazine	10 g
(2)	lactose	90 g
(3)	corn starch	29 g
(4)	magnesium stearate	1 g
1000 tablets		130 g

(1), (2) and 17 g of corn starch were mixed, and granulated with a paste made from 7g of corn starch. To the granulate was added 5 g of corn starch and (4), and the mixture was

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